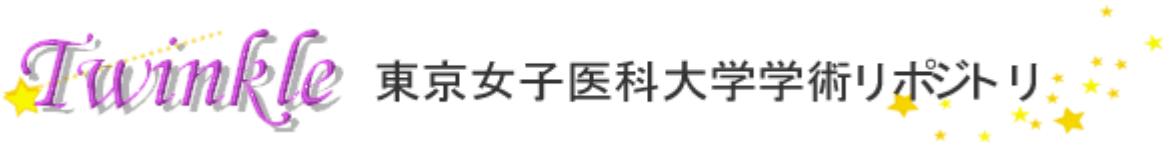

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ORIGINAL ARTICLE

Serum non-high-density lipoprotein cholesterol (non-HDL-C) levels and cardiovascular mortality in chronic hemodialysis patients

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Abstract
Background Non-high-density lipoprotein cholesterol (non-HDL-C) has been proposed as a predictor of cardiovascular disease (CVD) in the general population. The aim of this study was to evaluate the utility of non-HDL-C in predicting CV mortality in chronic hemodialysis (HD) patients.
Methods We calculated the serum non-HDL-C level of 259 HD patients by subtracting their HDL-C levels from their total cholesterol. Cox proportional hazards models were used to estimate the hazards ratio (HR) for CV mortality and the 95% confidence interval (CI). A receiver-operating characteristic (ROC) analysis was performed to estimate the relationship between sensitivity and specificity of a diagnostic parameter.
Results There were 44 deaths (17.0%) during the follow-up period, 33 (12.7%) of which were due to CVD. A multivariate Cox analysis with adjustments for age, diabetes, dialysis vintage, systolic blood pressure, serum albumin, and lipid levels showed that non-HDL-C was an independent predictor of CV mortality (HR 1.015, 95% CI 1.004–1.025, $p = 0.0083$). An ROC analysis showed that the plots of the non-HDL-C levels yielded significant specificity and sensitivity for predicting the risk of CVD mortality in HD patients [area under the curve (AUC) 0.62416; $p = 0.0366$; cutoff value 111.0 mg/dl]. The Kaplan–Meier survival curves of HD patients showed significant differences in CV mortality according to their tertiles with respect to serum non-HDL-C levels ($p = 0.0165$).
Conclusion The results of this study suggest that serum non-HDL-C level is a significant CV mortality predictor of chronic HD patients.

Keywords: Cardiovascular disease · Dyslipidemia · Non-HDL cholesterol · Mortality · Hemodialysis

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Introduction

Cardiovascular disease (CVD) is the primary cause of death of end-stage renal disease (ESRD) patients in Japan [1], and intensive management of CV risk factors, including dyslipidemia, has been proposed in order to reduce the burden of CVD in hemodialysis (HD) patients. Most HD patients have normal total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels, but HD patients tend to have low high-density lipoprotein cholesterol (HDL-C) and high triglyceride (TG) levels [2]. Guidelines for the management of patients with dyslipidemia and chronic kidney disease have recently been published [3], and the algorithms in the guidelines are based on fasting lipid profile data, which can be difficult to obtain in patients with diabetes mellitis (DM) and patients on an afternoon or nighttime dialysis schedule.

The serum non-HDL-C level is the sum of the LDL-C, intermediate-density lipoprotein-C, and very-LDL-C levels, and as the non-HDL-C levels are strongly correlated

with apolipoprotein B (ApoB) levels, it has been suggested that non-HDL-C levels may be a better marker of atherogenic cholesterol than LDL-C levels [4]. The non-HDL-C level can be easily calculated by subtracting the HDL-C level from the TC level. Non-HDL-C levels have been found to be a predictor of CVD in the general population [5], and as TC and HDL-C data are similar, whether measured in the fasting or nonfasting state, non-HDL-C is a reliable marker for use in the general population. However, the role of non-HDL-C in the mortality of HD patients has not been extensively investigated [6]. The aim of this study was to evaluate the utility of serum non-HDL-C level in predicting CV mortality in chronic HD patients.

Materials and methods

This was a prospective cohort study conducted at the Kidney Center of Hidaka Hospital in Takasaki, Japan. Exclusion criteria were inability to give informed consent, septicemia, and hospitalization for severe illness. We also excluded patients <30 years and >90 years, patients whose lipid data were unavailable, and patients who had a past history of CVD based on their medical records, including myocardial infarction (MI), congestive heart failure (CHF), peripheral arterial disease (PAD), and/or stroke. The 259 remaining chronic HD patients (HD duration >6 months) gave their consent to participate in this study. No patient had an acute infection or malignancy at entry into the study. We measured their baseline parameters in January 2006 and followed them up until September 2011. This study was approved by the ethics review committee of the hospital, and it was conducted in compliance with the Declaration of Helsinki.

All patients had been on regular HD, 4–5 h each time, three times a week at a blood flow rate of 180–200 ml/min via their arteriovenous fistulas. A bicarbonate dialysate was used at a flow rate of 500 ml/min in every patient. All HD sessions were performed using a high-flux polysulfone membrane dialyzer (BS-U, Toray Medical, Tokyo, Japan or APA, Asahi Medical, Tokyo, Japan). No bacteria or pyrogens grew out of the dialysate prepared from water obtained by reverse osmosis. An endotoxin removal filter was used to maintain the endotoxin concentration <0.020 EU/ml. A blood sample was drawn at the start and end of the dialysis session after 2-day interval. Blood was drawn just before the start of a dialysis session. Blood samples were collected after the patients had fasted for at least 9 h. Serum albumin, TC, HDL-C, LDL-C, TG, and C-reactive protein (CRP) were measured by routine laboratory methods. When the TG level was <400 mg/dl, the LDL-C level was calculated by using the Friedewald equation (LDL = TC − HDL − TG/5) [7]. The non-HDL-C level was calculated by subtracting the HDL-C from the TC level. Lipid value means were obtained from three measurements during the 3 months after entry. DM was diagnosed based on the World Health Organization (WHO) criteria [8]. The clinical status of each patient was evaluated by a routine clinical examination before the regular HD session. Systolic blood pressure (BP) was measured with a mercury sphygmomanometer after the patient rested in the supine position for 10–15 min, and mean values of 1 month measurements were used in the analysis. Information on treatment with statins was collected from the medical records.

Data are expressed as the mean ± standard deviation (SD). Patient-years were calculated from data of the baseline examination and the date of death due to CVD during the follow-up period. Cox proportional hazards models were used to estimate the hazards ratio (HR) for CV mortality and the 95% confidence interval (CI), with adjustment for age, DM, dialysis vintage, systolic BP, and serum albumin levels. All variables with a p value <0.1 in the univariate analysis were included in the multivariate regression model. Survival was estimated on the basis of the Kaplan–Meier curves and compared using the log-rank test. A receiver-operating characteristic (ROC) analysis was performed. ROC curves are graphic representations of the relationship between sensitivity and specificity of a diagnostic parameter and are drawn through potential points that represent different decision levels. The area under the ROC curve (AUC) is a measure of the performance of the test, and the larger the AUC, the better the test performance. All statistical calculations were performed using JMP version 9.0.1 software (SAS Institute Japan, Tokyo, Japan); p values <0.05 were considered statistically significant.

Results

During the 5-year follow-up period, we ultimately analyzed data of 259 patients. Table 1 shows baseline characteristics of participants, who consisted of 165 men and 94 women with a mean age of 61.3 ± 11.9 years. Mean duration of HD therapy was 10.9 ± 8.5 years. The cause of their ESRD was primary renal disease in 197 patients and DM in 62 patients. The residual urine output of all patients was within 100 ml/day. Fourteen patients (5.4%) were treated with statins during the follow-up period. The mean serum albumin and CRP levels were 3.7 ± 0.3 g/dl and 0.4 ± 0.8 mg/dl, respectively.

During the follow-up period, 44 patients (17.0%) died, and 33 (12.7%) of the deaths were due to CVD. The CVD was CHF in 19 patients, acute MI in six, PAD in three, stroke in two, cardiac sudden death in two, and pulmonary

Table 1 Baseline characteristic of the study population

Patient characteristics	
Number	259
Age (years)	61.3 ± 11.9 (31–90)
Men	165 (63.7%)
Smoker	28 (10.8%)
Dialysis vintage (years)	10.9 ± 8.5 (0.6–33.7)
Diabetes mellitus	62 (23.9%)
Body mass index (kg/m^2)	21.4 ± 3.9 (6.7–44.7)
Systolic BP (mmHg)	138.7 ± 22.7 (75–208)
Hemoglobin (g/dl)	10.2 ± 1.0 (7.5–13.5)
Albumin (g/dl)	3.7 ± 0.3 (2.7–4.5)
C-reactive protein (mg/dl)	0.4 ± 0.8 (0–7)
Phosphorus (mg/dl)	6.0 ± 0.8 (5.2–6.8)
TC (mg/dl)	151.0 ± 33.1 (63–246)
LDL-C (mg/dl)	84.8 ± 27.5 (19–187)
HDL-C (mg/dl)	44.0 ± 13.3 (18–92)
Non-HDL-C (mg/dl)	107.0 ± 32.0 (36–207)
Triglyceride (mg/dl)	110.9 ± 63.5 (33–457)
Statins	14 (5.4%)

CVD cardiovascular disease, *BP* blood pressure, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol = TC − HDL-C

hypertension in one. The non-CVD causes of death consisted of sepsis in five patients, pneumonia in two, peritonitis in one, gastrointestinal perforation in one, malignancy in one, and gastrointestinal bleeding in one. Table 2 shows the results of univariate Cox proportional hazards analysis for predictors of CV mortality. Univariate analysis revealed that the following characteristics were significantly associated with higher CV mortality rates: older age, presence of DM, shorter dialysis vintage, higher systolic BP, lower serum albumin levels, and higher non-HDL levels. As shown in Table 3, a multivariate analysis with adjustments for age, DM, dialysis vintage, systolic BP, and serum albumin and lipid levels showed that non-HDL-C was an independent predictor of CV mortality (HR 1.015, 95% CI 1.004–1.025, $p = 0.0083$) and the HR of non-HDL-C was similar to those of TG (HR 1.008, 95% CI 1.002–1.013, $p = 0.0078$).

To identify the lipid parameters of HD patients that were the best marker of CV mortality, an ROC analysis was performed. The plots of non-HDL-C in Fig. 1 show the similar specificity and sensitivity for evaluating CVD mortality in HD patients (AUC 0.62416; $p = 0.0366$; cutoff value 111.0 mg/dl). Even though the AUC values of TC and LDL-C were similar to those of non-HDL-C, there was no statistically significant difference according to each cutoff point.

Patients were divided into tertiles according to their serum non-HDL-C levels, as follows: T1 ≤90 mg/dl; T2 91–115 mg/dl; T3 ≥116 mg/dl. As shown in Fig. 2, the Kaplan–Meier survival curves of HD patients showed significant differences in CV mortality between tertiles with respect to serum non-HDL-C levels ($p = 0.0165$). Survival rate in the highest tertile (non-HDL-C ≥116 mg/dl) was significantly higher than in the other two tertiles (non-HDL-C ≤115 mg/dl).

Table 2 Univariate Cox proportional hazards analysis showing predictors of cardiovascular mortality in the study population

	HR	95% CI	*p* value
Age	1.056	1.024–0.089	0.0004
Gender (male)	1.173	0.581–2.511	0.6635
Diabetes	3.121	1.551–6.194	0.0018
Dialysis vintage	0.938	0.888–0.984	0.0067
Body mass index	1.011	0.919–1.091	0.8114
Systolic blood pressure	1.017	1.001–1.032	0.0354
Hemoglobin	0.909	0.634–1.296	0.6017
Albumin	0.288	0.106–0.817	0.0197
Phosphorus	0.889	0.665–1.181	0.4207
C-reactive protein	1.276	0.884–1.614	0.1625
TC	1.009	0.999–1.019	0.0738
HDL-C	0.989	0.962–1.017	0.4375
LDL-C	1.010	0.999–1.022	0.0739
Non-HDL-C	1.011	1.001–1.021	0.0280
Triglyceride	1.004	0.999–1.009	0.0803

HR hazards ratio, *CI* confidence interval, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-densitylipoprotein cholesterol = TC − HDL-C

Table 3 Multivariate Cox proportional hazards analysis showing predictors of cardiovascular mortality in the study population

	HR	95% CI	*p* value
Age	1.064	1.026–1.105	0.0008
Diabetes	3.660	1.507–8.927	0.0044
Dialysis vintage	0.984	0.928–1.038	0.5690
Systolic blood pressure	0.999	0.983–1.016	0.9487
Albumin	0.444	0.124–1.604	0.2147
TC	1.013	1.003–1.023	0.0106
LDL-C	1.013	1.000–1.025	0.0514
Non-HDL-C	1.015	1.004–1.025	0.0083
Triglyceride	1.008	1.002–1.013	0.0078

HR hazards ratio, *CI* confidence interval, *Non-HDL-C* non-high-density lipoprotein cholesterol = TC − HDL-C

Discussion

The results of this study showed that serum non-HDL-C level was an independent predictor of CV mortality in

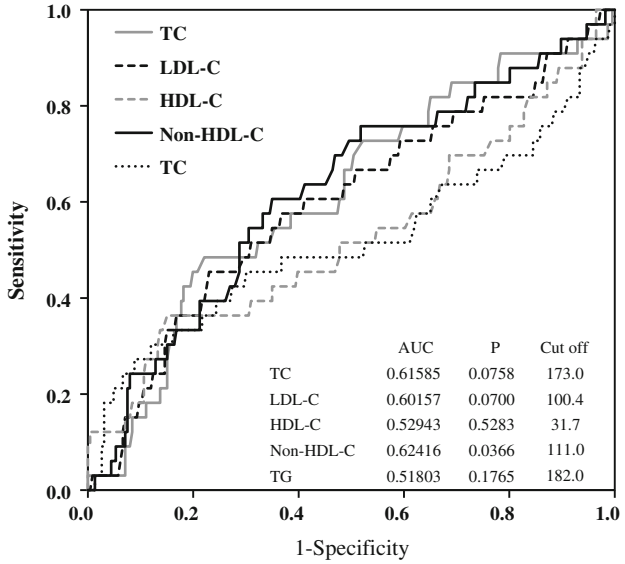

Fig. 1 Receiver-operating characteristic (ROC) curves for individual lipid parameters based on cardiovascular mortality of 259 hemodialysis patients

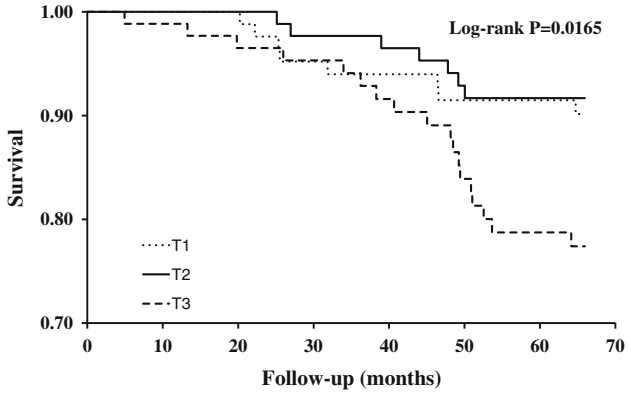

Fig. 2 Overall survival curves of hemodialysis patients according to tertile with respect to serum non-high-density lipoprotein cholesterol (non-HDL-C) level. T1 ≤90 mg/dl; T2 91–115 mg/dl; T3 ≥116 mg/dl

chronic HD patients and that non-HDL-C was a significant marker of CV mortality in a cohort of HD patients. These results were consistent with the epidemiology in the general population.

Liu et al. [9] reported that serum non-HDL-C level is a stronger predictor of coronary heart disease risk than the serum LDL-C level based on data sets from the Framingham Heart Study (2,693 men; 3,101 women). In the Suita study, a total of 4,694 men and women aged 30–74 years with no history of CVD or use of lipid-lowering medication, a fasting blood sample was collected, and they were followed up for 11.9 years [10]. During the follow-up period, there were 80 incident MIs and 139 strokes. The HR for MI was higher (2.97; 95% CI 1.26–6.97) for the top quintile according to serum non-HDL-C levels (≥180 mg/dl in men and ≥189 mg/dl in women) compared with the lowest quintile (<123 mg/dl in men and <143 mg/dl in women). Analysis of trends showed a significant positive relationship between MI incidence and serum non-HDL-C levels ($p = 0.02$). More recently, Kitamura et al. [11] analyzed data from 8,132 adults aged 40–69 years with no history of stroke or coronary heart disease and found that higher serum non-HDL-C levels were associated with an increased risk of coronary heart disease. Thus, serum non-HDL-C levels have been found to be an independent predictor of CVD in the general population.

Nishizawa et al. [12] reported for the first time that non-HDL-C is an independent predictor of CV mortality based on the Kaplan–Meier curves of a cohort of HD patients, but because the authors were unable to obtain sufficient information on CV mortality at baseline, pre-existing CVD may have confounded the results of an association between serum non-HDL-C and CV deaths during the follow-up period. In this study, we performed ROC analysis according to each cutoff value of serum lipids in order to evaluate the sensitivity and specificity of a diagnostic parameter. Moreover, Shoji et al. [13] performed an observational study of 45,390 HD patients with no history of MI or stroke at the end of 2003, extracted from a nationwide dialysis registry in Japan, in which a multivariate logistic regression analysis showed that incident MI was positively associated with non-HDL-C and inversely with HDL-C during a 1-year follow-up period. Among patients who experienced a new MI or stroke, the risk of death was not associated with their serum HDL-C or non-HDL-C levels but with older age, lower BMI, and higher CRP levels, suggesting that dyslipidemia was associated with increased risk of incident atherosclerotic CVD and that protein energy wasting and inflammation were associated with increased risk of death after CVD events.

The serum non-HDL-C level is the sum of the LDL-C, intermediate-density lipoprotein-C, and very-LDL-C levels, and serum non-HDL-C levels are strongly correlated with ApoB levels. It has therefore been suggested that non-HDL-C levels may be a better marker of atherogenic cholesterol than LDL-C levels [4]. The non-HDL-C level can be calculated easily by subtracting the HDL-C level from the TC level. As TC and HDL-C data are similar whether measured in the fasting or nonfasting state, non-HDL-C is a reliable measure for HD patients [14, 15]. Because LDL-C data are calculated using the Friedewald equation, elevated TG levels, even in the fasting state, result in LDL-C levels that may not reflect the atherogenic burden. Wanner and Krane [16] suggested that the non-HDL-C level should be used as the primary target of treatment in HD patients and that the non-HDL-C level is an integrated index for atherogenic lipoproteins and is unaffected by eating.

Although epidemiological studies have shown that treatment of HD patients with statins is accompanied by lower CV mortality [17–19], prospective, randomized trials of the potential beneficial effect of statins in this patient population have yielded disappointing results. In this study, statins were prescribed to CKD patients when their serum LDL-C levels were >130 mg/dl. The Die Deutsche Diabetes Dialyse (4D) trial enrolled 1,255 diabetic HD patients and randomized them to receive either placebo or 20 mg/day of atorvastatin [20], but after a mean follow-up period of 2.4 years, atorvastatin had not significantly reduced the risk of the composite primary end point (CV death, nonfatal MI, and stroke), despite a significant 42% reduction in LDL-C concentration [21]. Several mechanisms have been proposed to explain the failure of statins to improve CV outcomes of HD patients. It has been suggested that the initiation and progression of atherosclerotic disease in this population may have a different pathophysiological basis, including arterial wall calcification and inflammation, whereas other investigators emphasize that lipoproteins other than LDL-C may play a significant role in the initiation and progression of coronary atherosclerosis [22, 23]. Further study is needed to elucidate the effect of statin therapy targeted at serum non-HDL-C levels in HD patients on their CV mortality.

There were several limitations to this study. First, sample size and number of events were small, and despite careful adjustments in our statistical analyses, it was impossible to rule out the presence of residual confounding factors. We used Cox regression models adjusted by serum albumin level as a covariate for malnutrition and inflammation, as previously reported [24]. Second, it is likely that the prevalence of CV events was lower, as study participants were relatively younger and included fewer diabetic patients. In addition, serum lipid levels of the study population were relatively low, including cases with an extremely low range. Third, CHF was a major cause of CV mortality, and it may not represent atherogenic CVD in HD patients. The inclusion of CHF as a cause of CV death may have diluted the role of atherogenic CVD in CV mortality. However, most CHF was based on ischemic heart disease accompanied by ST-T changes on the electrocardiogram (data not shown). Taking these limitations into consideration, the results of this study do not conflict with the relationship between serum non-HDL-C levels and CV mortality.

Conclusion

The results of this study show that serum non-HDL-C level is a significant predictor of 5-year CV mortality in chronic HD patients. A better understanding of the biological role of non-HDL-C is needed to corroborate its suitability as a target of lipid-lowering therapy in HD patients.

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Conflict of interest None.

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